II. REMARKS

Preliminary Remarks

Reconsideration and allowance of the present application based on the following remarks are respectfully requested. Claims 38-128 are currently pending and remain at issue in this application. This response is timely filed as it is accompanied by a petition for an extension of time to file in the third month and the requisite fee.

On page 2 of the specification, the examiner objected to the specification for lacking a brief description of the drawings' section. The applicants hereby submit that description of Figure 1 has been added on page 6, line 9 of the specification. In view of the foregoing amendment, the applicants hereby submit that the objection to the specification has been overcome and should be withdrawn.

In paragraph 1 of the official action, the examiner objected to claims 87, 88, 95, 96, 103, 104, 111, and 112 for allegedly being awkward. Specifically, the examiner alleged that the phrase "for from" should be reworded. The applicants hereby submit that the word "from" has been removed from the phrase "for from" in claims 87, 88, 95, 96, 103, 104, 111, and 112, thus rendering the objection moot. The applicants do not intend by these or any amendments to abandon subject matter of the claims as originally filed or later presented, and reserve the right to pursue such subject matter in continuing applications.

Patentability Remarks

Rejection Pursuant to 35 U.S.C. §112, Second Paragraph

In paragraph 2 of the official action, the examiner rejected claims 53-56 under 35 U.S.C. §112, second paragraph for allegedly being indefinite. Specifically, the examiner alleged that the phrase "LHRH antagonist" in claims 53-56 lack proper antecedent basis.

Solely to expedite prosecution and without prejudice to the applicants' right to seek broader claims in a continuing application, claims 54 and 55 have been canceled without prejudice. The applicants respectfully submit that the phrase "LHRH antagonist" in claims 53 and 56 has been amended to use the phrase "Cetrorelix," which has proper antecedent basis in claim 51. In view of the foregoing amendment, the rejection of claims 53-56 under 35 U.S.C. §112, second paragraph, has been overcome and should be withdrawn.

Rejection Pursuant to 35 U.S.C. §102(a)

In paragraph 3 of the official action, the examiner rejected claims 38, 39, 41-43, 46-52, 54, 55, 58-62, 64-66, 69-74, 76, 77, and 80-82 under 35 U.S.C. §102(b) as being anticipated by Oliveness, *et al.*, *Fertil. Steril.* 62:468-473 (1994) (hereafter "Oliveness"). Specifically, the examiner alleged that Oliveness discloses that the LHRH antagonist Cetrorelix, in a single or dual administration protocol, was able to prevent LH surging in all of the 17 patients studied. The examiner further asserted that Oliveness teaches a method of carrying out controlled ovarian hyperstimulation in 17 women wherein an amount of the exogenous gonadotropin hMG is administered to the women starting on day 2 of the menstrual cycle. The examiner further asserted that doses of 5 mg of Cetrorelix is then administered subcutaneously. The examiner further alleged that plasma LH levels exhibited a marked decrease and remained low after the administration of LH.

Solely to expedite prosecution, and without prejudice to seeking broader claims in a continuing application, the applicants have canceled claims 41, 43, 54, 55, 64, 66, 76, and 77 without prejudice. The applicants submit that Oliveness fails to teach a method for obtaining the production of a fertilizable oocyte within a program of controlled ovarian stimulation for assisted reproduction techniques (COS/ART) comprising (a) administering an exogenous gonadotropin to induce follicle growth, and (b) administering a luteinizing hormone releasing hormone (LHRH) antagonist to prevent a premature LH surge, wherein the LHRH antagonist is administered in a single or dual dosage regimen of 1 to 10 mg per dose beginning on menstruation cycle day 1 to 10.

The applicants submit that Oliveness' procedure is cumbersome and lacks a predictable schedule for producing a fertilizable oocyte for assisted reproductive techniques. Under the requirements of Oliveness' method, choosing the precise day to initiate treatment with Cetrorelix cannot occur until estrodiol levels reach between 150 and 200 pg/ml in the female candidate's blood serum and her follicles of interest must be greater than or equal to 14 mm. The estradiol and follicle monitoring thus requires two steps in contrast to the applicants' claimed invention. First, a woman's blood plasma must be obtained each day during the first half of the menstrual cycle to determine the concentration of estradiol. The blood work allows physicians to monitor estradiol levels that begin at 40 pg/ml at cycle day 1 and non-incrementally increase to a range of 150-400 pg/ml/per follicle the day of ovulation.

The precise day estradiol levels reach 150 pg/ml is different for each woman and thus it is difficult to predict when the critical concentration of estradiol (150 pg/ml) will be reached. Secondly, Oliveness also requires an ultrasound be performed each day to identify the number of maturing follicle that are reaching a size of greater than or equal to 14 mm.[1] Oliveness teaches that 5 mg of the LHRH antagonist Cetrorelix is administered only when both parameters (i.e., estradiol levels are 150 pg/ml per follicle 14mm or greater) are satisfied. Therefore, using the method of Oliveness, it is impossible to provide a standardized schedule for producing a fertilizable oocyte for application to assisted reproductive techniques.

Oliveness' method is problematic with regard to relying on measuring estradiol in a woman's blood plasma as well. The applicants submit that values differ significantly when using different methods to determine estradiol levels in the blood plasma. In addition, the measurement of follicle size requires using an ultrasound, which is not an ordinary skill in the art and requires a lot of experience. Accordingly, following the criteria set forth in Oliveness, the first dose of Cetrorelix could be injected either too early, which would prevent the LH surge, or too late, which would interfere with proper implantation of a viable egg.

In stark contrast, the applicants invention does not require the onerous steps of drawing blood from a female patient from day 2 onward and performing ultasounds to determine follicle size. The applicants claimed invention (i.e., 38, 39, 41-43, 46-52, 54, 55, 58-62, 64-66, 69-74, 76, 77, and 80-82) simply requires a scheduling of either a single or dual dose regimen of LHRH antagonists between days 1 and 10 of the menstrual cycle in conjunction with administering exogenous gonadotropin to induce follicle growth. The applicants have unexpectedly determined that doses of an LHRH antagonist (ranging from 1 to 10 mgs) can be administered as early as day 1 and as late as day 10 of the menstrual cycle, wherein the LH surge is prevented, FSH secretion is maintained at a natural level (unlike Oliveness, see page 470), ovulation occurs between day 9 and 20 of the menstrual cycle, and a fertilizable oocyte is produced for application to assisted reproductive techniques. The applicants' claimed invention allows for a predictable schedule for controlled ovarian stimulation and assisted reproductive techniques to occur between a Monday and Friday. The

[1] Oliveness uses an equation requiring the absolute concentration of estradiol divided by the number of follicles.

female patient also only requires a visit to the clinic the day assisted reproductive techniques are to be performed instead of each day receiving a blood test and an ultrasound as required by Oliveness. Accordingly, Oliveness does not anticipate the applicants' streamlined method. In view of the foregoing amendment and remarks, the applicants submit that the rejection of claims 38, 39, 41-43, 46-52, 54, 55, 58-62, 64-66, 69-74, 76, 77, and 80-82 under 35 U.S.C. §102(b) as being anticipated by Oliveness has been overcome and should be withdrawn.

Rejection Pursuant to 35 U.S.C. §103(a)

In paragraphs 4 of the official action, the examiner rejected claims 40, 44, 45, 53, 56, 57, 63, 67, 68, 75, 78, 79, and 83-128 under 35 U.S.C. §103(a) as being unpatentable over Oliveness *et al.* in view of Reismann *et al.*, *Human Reproduction* 10:1974-1981 (1995)(hereafter Reismann). The examiner alleged that although Oliveness does not disclose administering 3 mg of Cetrorelix or administering Cetrorelix starting cycle day 4-8 or 6-10, Reismann discloses a study in which patients were stimulated with HMG, and on cycling day 7, cetrorelix was administered subcutaneously to the patients. The examiner further asserted Reismann showed that three hours before inducing ovulation, LH measurements showed a decrease in LH levels. The examiner also asserted that Reismann discusses a study regarding Cetrorelix being administered daily from cycle day 7 until induction of ovulation (page 1978, third full paragraph). The examiner concluded that it would have been obvious to one of skill to modify the method of Oliveness to produce fertilizable oocytes by administering 3 mg of Cetrorelix from cycle day 7 onward because they would reasonable expect such a lower dosage and administration starting point to prevent premature LH surges.

The examiner also asserted that modifying the amount of Cetrorelix administered to prevent premature LH surges could be correlated by the teachings of Reismann *et al.* since this reference established a correlation between the amount of cetrorelix administered and resulting plasma LH levels (page 1978, third full paragraph). With respect to claim 115, the examiner alleged it would have been obvious to administrate HMG because one of skill expects the administration of cetrorelix to achieve the prevention of unwanted premature LH surges while allowing for normal follicular growth. The examiner further alleged that the claimed daily dosages are obvious to one of skill to prevent unwanted LH surges, which prevent follicular growth to occur. Finally, the examiner asserted that claims 124, 125, 127,

and 128 would be obvious in view of the cited references since extracorporeal fertilization by sperm injection as well as *in vitro* fertilization is a conventional means of producing fertilizable oocytes.

A *prima facie* case of obviousness requires: (1) some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) the teaching or suggestion of all the claim limitations of the applicants' invention in the combined prior art references; and (3) a reasonable expectation of success. M.P.E.P. § 2143. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure." *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Moreover, the prior art must provide some teaching, suggestion or motivation to make the **specific** combination that was made by the applicant." *In re Dance*, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998) (emphasis added) (citing *In re Raynes*, 7 F.3d 1037, 1039, 28 USPQ2d 1630, 1631 (Fed. Cir. 1993); *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992).

The applicants submit that the primary reference, Oliveness, fails to teach or suggest a method for obtaining the production of a fertilizable oocyte within a program of controlled ovarian stimulation for assisted reproduction techniques (COS/ART) comprising (a) administering an exogenous gonadotropin to induce follicle growth; and (b) administering a LHRH antagonist to prevent a premature LH surge, wherein the LHRH antagonist is administered in a simple or dual dose regimen of 3 mg or a multiple dose regimen of 0.25 mg beginning on menstrual cycle day 1 to 10. Specifically, Oliveness teaches a cumbersome method for determining the appropriate time to inject Cetrorelix through the monitoring of a woman's estradiol levels and determining the size of maturing follicles during the first half of the menstrual cycle. Oliveness also teaches 5 mg injections of Cetrorelix in a single or dual dose regimen can only occur when both parameters (*i.e.*, estradiol levels reach 150 pg/ml and maturing follicles are 14 mm or greater) are satisfied. Therefore Oliveness makes it impossible to set up a standardized or predictable schedule for controlled ovarian stimulation and assisted reproductive techniques. The applicants submit that nowhere in the teachings of Oliveness is there a discussion or suggestion of simply administering single, dual, or multiple regimens of LHRH antagonists at levels of 3 mg or lower between days 1 and 10 of the

menstrual cycle without the onerous steps of taking blood plasma and performing ultrasounds for each female patient each day until the right conditions are present (*i.e.*, estradiol levels reach 150 pg/ml and maturing follicles are 14 mm or greater).

The applicants method as directed in the claimed invention removes the daily monitoring of a females estradiol levels and maturing follicles for a less cumbersome, predictable time table by administering an LHRH antagonist on a given day based on the clinics' schedule and not the estradiol levels of a female candidate. The applicants method of administering LHRH antagonists, like Cetrorelix, not only controls LH surge, but also was found to produce a fertilizable oocyte, and maintain FSH levels at a natural level. In stark contrast, Oliveness' method requires the female candidate for assisted reproductive techniques to visit the clinic each day to receive a blood test and ultrasound in order to administer Cetrorelix when estradiol levels are 150 pg/ml or higher and each mature follicle is 14mm or greater. Therefore, one of skill in the art, studying the disclosure of Oliveness in view of the stark contradictions, would not be taught or even suggested to practice the claimed invention.

With regard to the secondary reference, Reissmann, the applicants respectfully submit that this reference does little to overcome the failings of the primary document (Oliveness), and, in fact, teaches away from the claimed invention. Specifically, Reissmann does not teach a multiple dose regimen as low as 0.25 mg/day even when starting on day 7 of the menstrual cycle. One of skill in the art at the time of Reissmann would not expect that lowering the daily dosage limit from 1 mg to 0.25 mg of Cetrorelix would be enough to prevent the estradiol effects on the LH surge. Reissmann fails to discuss that LHRH antagonist levels as low as 0.25 mg would be able to prevent an LH surge despite escalating levels of estradiol leading up to an LH surge and its' effect on increasing endogenous LH values. The applicants submit that Reissman fails to teach or suggest that LHRH antagonist at levels as low as 0.25 mg administered daily can still out compete the estradiol effect on LH levels. Thus, the applicants submit it was not within the skills of one at the time of filing the application that a daily dosage of 0.25 mg of LHRH antagonist would be able to dampen the rising estradiol concentrations leading to an LH surge.

The applicants further submit that Reissmann's recommended daily dosage of 1 mg or 3 mg starting at day 7 could have detrimental effects on successful implantation for a viable

pregnancy to occur. Specifically, due to the pharmaceutical formulations of Cetrorelix, a gel is formed during the subcutaneous injections of the LHRH antagonist. Reissmann's recommended dosage of either 1 mg or 3 mg of Cetrorelix actually causes each injection to last up to 4 days longer than a 0.25 mg dose. In stark contrast, the applicants 0.25 mg dosage of an LHRH antagonist immediately goes into the bloodstream and prevents an LH surge. The consequence of Reissmann's formulations is a overhang of LHRH antagonist in the bloodstream at the time of COS/ART procedures which would have detrimental effects on embryo transfer and successful implantation. At the time of filing, Reissmann failed to teach or suggest that dosages as low as 0.25 mg would still prevent LH surges. As discussed above, in view of the teachings of Oliveness, moving Cetrorelix treatment up to the 7th day of the menstrual cycle using a multiple dose schedule still requires the monitoring steps required by Oliveness and the high concentrations of the daily doses taught by Reismann. Accordingly, either alone or in combination, both of these teachings would still increase the chances of preventing a successful implantation. The applicants' claimed invention does not require the monitoring of estradiol levels or follicular sizes. The applicants' claimed method (40, 44, 45, 53, 56, 57, 63, 67, 68, 75, 78, 79, 83, 84, 86-92, 94-100, 102-108, 110-116, and 118-128) also unexpectedly discovered that daily dosages as low as 0.25 mg could be successful at controlling LH surges while allowing predictable scheduling of controlled ovarian stimulation and assisted reproductive techniques to occur.

In conclusion, the applicants submit that Oliveness either alone or in combination with Reissmann neither teach nor suggest the applicants' claimed invention. Accordingly, without such teaching or suggestion, the examiner has not established a prima facie case of obviousness. Solely to expedite prosecution and without prejudice of seeing broader claims in a continuing application, the applicants have canceled claims 85, 93, 101, 109, and 117. In view of the foregoing amendment and remarks, the applicants respectfully submit that the rejection of 40, 44, 45, 53, 56, 57, 63, 67, 68, 75, 78, 79, and 83-128 under 35 U.S.C. §103(a) has been overcome, and should be withdrawn.

III. CONCLUSION

In view of the foregoing, the applicants believe that the claims are in form for allowance, and hereby respectfully solicit such action. If any point remains in issue which the examiner feels may be best resolved through a personal or telephone interview, the examiner is strongly urged to contact the undersigned at the telephone number listed below.

Respectfully submitted,

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